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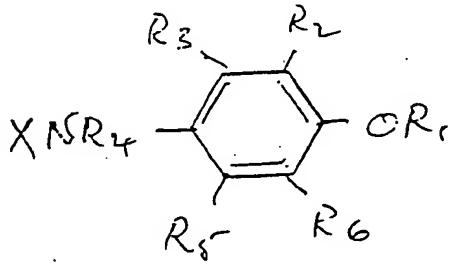

(I)

(57) Abstract

There are disclosed compounds of formula (I); in which R_1 represents C(O)YZ or SO_2R_{10}, Y represents a single bond, O, NR_{11} or CO, Z represents hydrogen, alkyl or alkyl substituted by one or more substituents selected from hydroxy, alkoxy, acyloxy, carboxy, alkoxycarbonyl, $CONR_{12}R_{13}$, arylalkoxy, Ar_1, heterocycle, halo, cyano or $NR_{14}R_{15}$, R_2, R_3, R_5 and R_6, which may be the same or different, represent hydrogen, alkyl, alkoxy or halogen, R_4 and R_{11}, which may be the same or different, represent hydrogen or alkyl, R_{10} represents alkyl, X represents a heterocycle optionally substituted by one or more substituents selected from alkyl, cycloalkyl, alkoxy, alkoxycarbonyl, carboxy, hydroxyalkyl, halo, $CONR_{16}R_{17}$, $NR_{18}R_{19}$, or Ar_2, Ar_1 and Ar_2 which may be the same or different represent aryl or aryl substituted by one or more substituents selected from halogen, nitro, alkoxy, carboxy, alkyl or trihaloalkyl, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19}, which may be the same or different, represent hydrogen, alkyl or benzyloxycarbonyl, or a pharmaceutically acceptable N-oxide, N-alkyl, salt, ester or amide derivative thereof, for use as a pharmaceutical, e.g. an anti-inflammatory agent.

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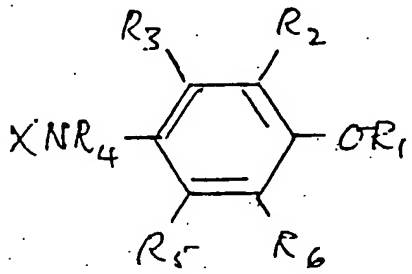
Anti-inflammatory 4-aminophenol derivatives

This invention relates to novel compounds, compositions thereof and methods for their preparation.

According to the invention there are provided compounds of formula I:



I

in which

R_1 represents C(O)YZ or SO_2R_{10},

Y represents a single bond, O, NR_{11} or CO,

Z represents hydrogen, alkyl or alkyl substituted by one or more substituents selected from hydroxy, alkoxy, acyloxy, carboxy, alkoxycarbonyl, $CONR_{12}R_{13}$, arylalkoxy, Ar_1, heterocycle, halo, cyano or $NR_{14}R_{15}$,

R_2, R_3, R_5 and R_6, which may be the same or different, represent hydrogen, alkyl, alkoxy or halogen,

R_4 and R_{11}, which may be the same or different, represent hydrogen or alkyl,

R_{10} represents alkyl,

X represents a heterocycle optionally substituted by one or more substituents selected from alkyl, cycloalkyl,

alkoxy, alkoxycarbonyl, carboxy, hydroxyalkyl, halo, $CONR_{16}R_{17}$, $NR_{18}R_{19}$, or Ar_2,

Ar_1 and Ar_2 which may be the same or different represent aryl or aryl substituted by one or more substituents selected from halogen, nitro, alkoxy, carboxy, alkyl or trihaloalkyl,

R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19}, which may be the same or different, represent hydrogen, alkyl or benzyloxycarbonyl,

or a pharmaceutically acceptable N-oxide, N-alkyl, salt, ester or amide derivative thereof,

for use as a pharmaceutical.

According to the invention there are also provided the novel compounds of formula I and derivatives thereof, as defined above, provided that at least one of R_2 and R_6 is other thatn hydrogen.

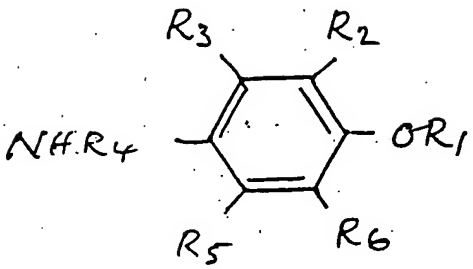
According to the invention there is further provided a process for the preparation of compounds of formula I which comprises

a) reacting a compound of formula II,

$$X\text{-}L_1 \qquad \text{II}$$

in which L_1 is a leaving group and X is as defined in Claim 1,

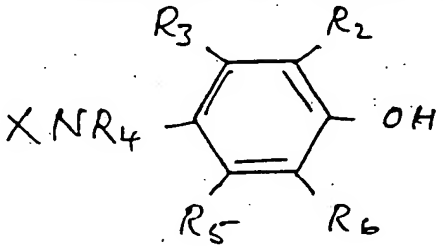
with a compound of formula III,



III

in which R_1, R_2, R_3, R_4, R_5 and R_6 are as defined in Claim 1,

b) reacting a compound of formula IV,



IV

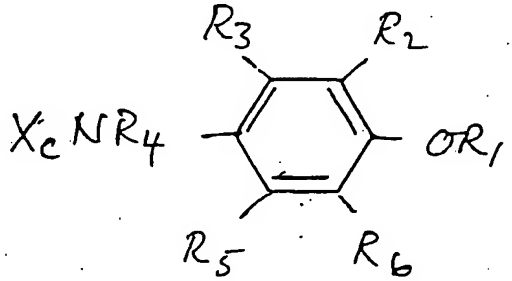
in which X, R_2, R_3, R_4, R_5 and R_6 are as defined above,

with a compound of formula V,

$$R_1L_2 \qquad V$$

in which L_2 is a leaving group and R_1 is as defined above,

c) producing a compound of formula I in which X represents an unsaturated heterocycle, by oxidising a corresponding compound of formula VI,



VI

in which Xc represents a corresponding heterocycle more saturated than X,

and R_1, R_2, R_3, R_4, R_5 and R_6 are as defined above,

d) producing a compound of formula I which bears one or more alkyl substituents containing at least two carbon atoms, by reducing a corresponding compound of formula I, in which the appropriate substituent(s) contains one or more double or treble carbon-carbon bonds,

e) producing a compound of formula I, in which X is substituted by cyclohexyl, by reducing a corresponding compound of formula I in which X is substituted by phenyl.

f) producing a compound of formula I substituted by one or more of OH, NHR_{14} or COOH, which comprises removing a protecting group from a corresponding compound of formula I bearing a protected OH, NHR_{14} or COOH group.

g) producing a compound of formula I, in which Z represents alkyl substituted by cyano, by reacting a corresponding compound of formula I in which Z represents alkyl substituted by halogen, with a cyanide salt,

h) producing a compound of formula I, which is a N-alkyl salt, by reacting a corresponding compound of formula I in which X represents a nitrogen containing heterocycle, with an alkylating agent,

and where desired or necessary converting the

resulting compound of formula I into a pharmaceutically acceptable N-oxide, N-acetyl, salt, ester or amide thereof, or vice versa.

In process (a), leaving groups that L_1 may represent include, for example, halogen, eg chlorine or bromine; arylsulphonyl; hydroxy and esters thereof; alkoxy, eg methoxy or ethoxy; dihalophosphonyl, eg dichloro- or dibromo-phosphonyl; and $-NR_aR_b$, where R_a and R_b may each independantly represent hydrogen or alkyl C1 to C6.

The reaction may be carried out with or without a solvent. When the reaction is carried out using a solvent, the solvent is preferably inert to the conditions of the reaction, and may be for example, a polar solvent such as 1,4-dioxan, ethanol, acetic acid, acetonitrile or dimethylformamide. However apolar solvents, eg toluene, may also be used. The reaction is preferably carried out at a temperature of from about 25 to 200°C.

In process (b), leaving groups that L_2 may represent include Oacyl (ie compound V is an acid anhydride), tosylate, mesylate, imidazolide, bromide or, preferably, chloride. The reaction may be carried out by mixing the reagents in anhydrous conditions in the presence of an inert solvent such as dichloromethane. When the reagent of formula V is an acid halide, the reaction is preferably carried out in the presence of a base such as triethyl-

amine and/or dimethylaminopyridine.

In certain cases, for example when both R_2 and R_6 represent bulky groups such as tertiary butyl, Schotten Baumann conditions, in which the reaction is carried out using a base strong enough to abstract a proton from the phenol of formula IV, give particularly good results. A particularly suitable base that may be mentioned is potassium tert-butoxide.

Oxidising agents that may be used in process (c) for the oxidation of heterocycles Xc include metal catalysts, organic and inorganic oxidising agents, hypohalites and peroxides. Preferred metal catalysts include palladium on charcoal in the presence or absence of air. Preferred inorganic oxidising agents include manganese dioxide and chromium trioxide. Suitable organic oxidising agents include peracids, eg 3-chloroperbenzoic acid, and easily reduced hydrogen acceptors, eg 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and organic hypohalites such as tertiary butyl hypochlorite. The oxidation may be carried out in a solvent which is inert to the reaction conditions. The choice of solvent depends on the compound to be oxidized and on the oxidizing agent. However, suitable solvents include halogenated hydrocarbons such as dichloromethane, alcohols, eg ethanol and aromatic hydrocarbons, eg toluene. The reaction may be carried out

at a temperature of about 0 to 150°C.

The reduction of process (d) may be carried out using hydrogen and an appropriate metal catalyst, for example 10% palladium or rhodium on an inert support, such as charcoal. The reaction may be carried out in an inert solvent, for example ethanol, at a pressure of from 1 to 10 atmospheres of hydrogen.

The reduction of process (e) may be carried out under conditions generally similar to those described above for process (d).

Removal of the protecting groups in process (f) depends on the nature of the protecting groups, but in general conventional techniques may be be employed, including acidic, basic, electrolytic, photolytic and particularly hydrogenolytic methods. Protecting groups which may be mentioned include benzyl (Bzl); benzyloxy-carbonyl (CBz) or butyloxycarbonyl (Boc). Benzyl protecting groups Bzl and CBz may be removed by hydrogenolysis, for example by reaction with hydrogen in a suitable solvent such as an alcohol in the presence of a transition metal catalyst such as palladium on carbon. The Boc protecting group may be removed by treatment with acid, eg trifluoroacetic acid.

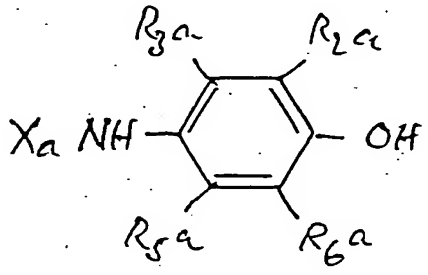
In process (g), the displacement of the halogen may be carried out in a solvent which is inert to the reaction

conditions. We particularly prefer a polar aprotic solvent, for example acetonitrile, dimethyl formamide or dimethyl sulphoxide. The reaction may be carried out at a temperature of from about 0 to 100°C.

The alkylation of process (h) may be carried out using an excess of the alkylating agent as slvent or using a solvent which is inert to the reaction conditions. We particularly prefer a polar aprotic solvent, for example acetonitrile, dimethyl formamide or dimethyl sulphoxide. The reaction may be carried out at a temperature of from about 0 to 100°C. Suitable alkylating agents include alkyl halides, for example, methyl iodide, and alkyl tosylates.

Compounds of formula II may be prepared from the corresponding 4-aminophenol, by the method of process b). Such 4-aminophenols are either known or may be made from known compounds using conventional methods.

Certain compounds of formula IV are known from either EP-A-254 259 or EP-A-178 035. Certain intermediates of formula IV are novel. Thus according to a further aspect of the invention there are provided compounds of formula IVa,



IVa

in which X_a represents 1H-pyrazol-3-yl substituted by 1-phenyl or 1-trifluromethylphenyl, R_2a and R_6a, which may be the same or different, are selected from lower alkyl, halogen and lower alkoxy, and both R_3a and R_5a represent hydrogen.

The novel phenols of formula IVa may be made by the methods indicated in the European applications cited above or by the methods described herein.

Compounds of formula VI may be prepared by methods analogous to those described in processes (a), (b), (d), (e), (f), (g) or (h).

The compounds of formulae II and V are either known or may be made from known compounds by conventional techniques known per se.

The acid addition salts of compounds of formula I may be prepared by reaction of the free base with an appropriate acid. The acid addition salts may be converted to the corresponding free base by the action of a stronger base.

The processes as described above may produce compounds of formula I or derivatives thereof. It is also within the scope of this invention to treat any derivative so produced to liberate the free compound of formula I, or to convert one derivative into another.

Pharmaceutically acceptable derivatives of compounds

of formula I include pharmaceutically acceptable acid addition salts. Suitable salts include salts of mineral acids, for example, hydrohalic acids, e.g. hydrochloric acid or hydrobromic acid, or organic acids, e.g. formic, acetic or lactic acids. The acid may be polybasic, for example sulphuric, fumaric or citric acid.

When the compound of formula I contains a carboxylic acid group, it may form pharmaceutically acceptable salt, ester and amide derivatives. Suitable salts include ammonium, alkali metal (eg sodium, potassium and lithium) and alkaline earth metal (eg calcium or magnesium) salts, and salts with suitable organic bases, eg salts with hydroxylamine, lower alkylamines such as methylamine or ethylamine, with substituted lower alkylamines, eg hydroxy substituted alkylamines such as tris(hydroxymethyl)methylamine or triethanolamine, with simple monocyclic nitrogen heterocyclic compounds, eg pyridine or morpholine, with an amino acid, eg lysine, ornithine, arginine, or an N-alkyl, especially an N-methyl derivative of any one thereof, or with an aminosugar, eg glucamine, N-methyl- glucamine or glucosamine. Suitable esters include simple lower alkyl esters, eg ethyl ester. esters derived from alcohols containing basic groups, eg bis-lower alkylamino substituted alkanols such as the 2-(diethylamino)ethyl ester, and acyloxy alkyl esters, eg a

lower acyloxy-lower alkyl ester such as the pivaloyloxymethyl ester. The pharmaceutically acceptable acid addition salts of the basic esters, eg the hydrochloride, the hydrobromide, the maleate or the fumarate salts, may also be used. The esters may be made by conventional techniques, eg esterification or transesterification. The amides may be, for example, unsubstituted or mono- or di- C1 to 6 alkyl or phenyl amides and may be made by conventional techniques, eg reaction of an ester of the corresponding acid with ammonia or an appropriate amine.

We prefer compounds of formula I in which R_1 represents C(O)YZ.

Particular values of Ar_1 that Z may represent include optionally substituted mono- and bicyclic aromatic species, for example naphthalene, and particularly, phenyl.

We prefer compounds in which Ar_1 is either unsubstituted or bears one substituent selected from halogen, eg chlorine, nitro, lower alkoxy, especially methoxy or carboxy.

When Z represents a heterocycle, the heterocycle may be unsubstituted or substituted by one or more substituents selected from alkyl, cycloalkyl, alkoxy, alkoxycarbonyl, carboxy, hydroxyalkyl, halo, $CONH_2$, NH_2 or phenyl. We prefer the heterocycle to be a 5- or 6- membered

heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur. Particular heterocycles that may be mentioned include furan, pyrrole, pyrazole, thiophene and especially pyridine. Suitable heterocyclic derivatives that Z may represent include pyridine N-oxide and N-alkyl pyridine, eg N-methyl pyridine.

When Y is O, we prefer Z to represent alkyl, especially lower alkyl, for example methyl, ethyl or butyl; or phenyl.

When Y is NR_{11}, we prefer Z to represent hydrogen or lower alkyl.

When Y is CO, we prefer Z to represent alkyl, eg lower alkyl such as methyl, ethyl or butyl.

However, we prefer compounds in which Y is a single bond. When Y is a single bond we prefer Z to be other than hydrogen. When Z represents alkyl, we prefer alkyl to represent lower alkyl, especially alkyl C1 to C4. The alkyl group may be saturated or unsaturated and straight or branched. Particular alkyl groups that may be mentioned include methyl, ethyl, n-propyl, iso propyl, n-butyl and tertbutyl. When the alkyl is substituted we prefer it to be tri-, di- and especially mono-substituted. The substituent(s) may be located on any part of the alkyl group. However we prefer those compounds which contain a single substituent located at the terminus of the alkyl

group, specific substituents that may be mentioned include hydroxy; lower alkoxy, eg methoxy or ethoxy; lower acyloxy, particularly C_1 to C_4 acyloxy, for example acetoxy, propanoyloxy; $CONH_2$; phenlyalkoxy, particularly phenylmethoxy; halogen, particularly bromine and especially chlorine; cyano or NH_2.

Particularly preferred groups that R_1 may represent include acetyl and acetyl subsituted by cyano or lower alkoxy.

We prefer compounds of formula I in which at least one of R_2, R_3, R_5 and R_6 is other than hydrogen. We particularly prefer those compounds in which at least two of R_2, R_3, R_5 and R_6 is other than hydrogen. Especially preferred are those compounds in which R_2 and R_6 are other than hydrogen. We prefer compounds in which at least one of R_2 and R_6 is alkyl. When one or more of R_2, R_3, R_4, R_5 or R_6 is alkyl, it may be saturated or unsaturated and straight or branched. We particularly prefer those compounds in which both R_2 and R_6 are alkyl, preferably lower alkyl, for example selected from methyl, ethyl, propyl, propenyl and butyl. Compounds in which R_2 and R_6 are the same are especially preferred. We also prefer compounds in which at least one, and preferably both, of R_3 and R_5 are hydrogen.

We prefer compounds in which R_4 is lower alkyl, eg methyl, ethyl or propyl, and especially hydrogen

We prefer compounds in which R_{10} is lower alkyl, and especially methyl, ethyl or propyl.

Substituents that R_{11} may particularly represent include hydrogen and lower alkyl, for example, methyl, ethyl or propyl.

Heterocycles that X may particularly represent may be unsubstituted or substituted by one, two or three substituents. The heterocycle may be saturated, partially saturated or fully unsaturated.

Heterocycles that may be particularly mentioned include those having a single or fused ring system, comprising from, for example, 2-4 rings and containing from one to five heteroatoms. Heteroatoms that may be particularly mentioned include nitrogen, oxygen and sulphur.

We prefer heterocycles having from 5 to 10 ring atoms. In particular, we prefer X to represent a 5- or 6- membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur.

Particular heterocyclic groups that X may represent include pyrroyl, furyl, thienyl, pyrazolyl, imidazolyl, benzimidazolyl, oxazolyl, isoxazolyl, triazolyl, thiadiazolyl, oxadiazolyl, triazinyl, pyrazinyl, pyridinyl,

quinolinyl, pyrimidinyl, pyridazinyl and tetrahydronaphtho-pyranyl.

Typical groups that X may represent include 1-pyrroyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1H-3-pyrazolyl, 2-imidazolyl, 2-benzimidazolyl, 2-oxazolyl, 4-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 1,2,3-triazoly-1-l, 1,2,3-triazoly-4-l, 1,2,4-thiadiazol-3-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, pyrazinyl, pyridin-2-yl, pyridin-4-yl, quinolin-2-yl, quinolin-4-yl, 2-pyrimidinyl, 4-pyrimidinyl, 3-pyridazinyl and 6,7,8,9-tetrahydronaphtho[2,3b]pyran-2-yl.

When X is substituted, we particularly prefer it to be substituted by three, two or most preferably, one substituent selected from alkyl, particularly lower alkyl, especially methyl, ethyl, propyl or butyl; cycloalkyl, eg cyclobutyl, cyclopentyl, cycloheptyl and particularly cyclohexyl; alkoxy, particularly lower alkoxy, especially alkoxy C1 to C4; alkoxycarbonyl, particularly lower alkoxycarbonyl, especially methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl and tert butoxycarbonyl; carboxy; hydroxyalkyl, particularly hydroxy lower alkyl including monohydroxy, C1 - C6 alkyl groups such as hydroxymethyl, 2-hydroxyethyl,

3-hydroxypropyl; halogen, including chlorine, fluorine, bromine and iodine; amino or Ar_2. Particular aryl groups that Ar_2 may represent include naphthalenyl and particularly phenyl, optionally substituted by three, two or, preferably, one substituent selected from halogen, eg chloro, fluoro or bromo; alkoxy, preferably lower alkoxy, eg methoxy or ethoxy; carboxy; alkyl, particularly lower alkyl, for example methyl, ethyl, propyl or trihaloalkyl, particularly trihaloloweralkyl, especially CF_3 or CH_2CF_3.

We particularly prefer those compounds in which X represents 1H-pyrazol-3-yl- optionally substituted by phenyl, especially 1-phenyl.

Compounds of formula I, and pharmaceutically acceptable derivatives thereof, are useful because they possess pharmacological activity in animals. In particular, the compounds are useful as broad spectrum anti-inflammatory agents as indicated in one or more of the following assay systems:

(a) Inhibition of lipoxygenases, e.g. 5, 12 and 15 lipoxygenase, in the presence of exogenous arachidonic acid and measurement of the enzyme activity by either a modification of B A Jakschik et al, Biochemical and Biophysical Research Communications, 95(1), 103, (1980) using reverse phase HPLC to quantify the products or by a

modification of the method of F F Sun et al, Prostaglandins 21 (2) 333 (1981) using uv absorption to quantify product formation.

(b) Inhibition of prostaglandin synthetase, utilising ovine seminal vesicle microsomes as the enzyme source after the method of Egan et al Biochemistry 17, 2230 (1978) using either radiolabelled arachidonic acid as substrate and product separation by thin layer chromatography and quantification by scintillation counting or unlabelled arachidonic acid as substrate and a specific radioimmunoassay kit (New England Nuclear) to measure prostaglandin E2 produced.

(c) Inhibition of 5 lipoxygenase activity in intact human neutrophils stimulated by ionophore A23187 and supplemented with exogenous arachidonic acid after the method of P Borgeat and B Samuelsson, Proceedings New York Academy of Science 70 2148 (1979) using reverse phase HPLC to measure the products.

(d) Inhibition of formation of arachidonic acid metabolites by mouse peritoneal macrophages challenged in vitro with immune complexes by the method of Blackham et al, J. Pharm. Pharmac. 37, 787, (1985).

(e) Inhibition of PGE2 formation and cell infiltration in the carrageenin sponge model by the method of Higgs et al, Eur. J. Pharmac. 66 81 (1980).

(f) Inhibition of immune complex mediated inflammation in the mouse peritoneal cavity by the method of Blackham et al, J. Pharmac. Methods 15, 77, (1985).

(g) Inhibition of carrageenin oedema in the rat by the method of Winter et al, Proc. Soc. Exp. Biol. 111 544 (1962).

(h) Inhibition of bronchial anaphylaxis in guinea pigs by the method of Anderson, Br. J. Pharmac. 77 301 (1982).

(i) Inhibition of oedema and eicosanoid production in mouse ears treated with arachidonic acid after the methods of Young et al, J. Invest. Derm. 82, 367, (1984) and Opas et al, J. Invest. Derm. 84, 253, (1985).

The compounds are indicated for use in the treatment or prophylaxis of inflammatory conditions in mammals, including man. Conditions that may be specifically mentioned are: rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, and other arthritic conditions, inflamed joints;

eczema, psoriasis, burns, including sunburn, ulcers, wounds, acne or other inflammatory skin conditions such as sunburn;

inflammatory eye conditions including conjunctivitis and uveitis; lung disorders in which inflammation is involved, eg asthma, bronchitis, pigeon fancier's disease and farmer's lung;

conditions of the ear including otitis externa;

conditions of the gastrointestinal tract including aphthous ulcers, gingivitis, Crohn's disease (a condition of the small, and sometimes also of the large intestine), atrophic gastritis and gastritis varialoforme (conditions of the stomach), ulcerative colitis (a condition of the large intestine and sometimes the small intestine) coeliac disease (a condition of the small intestine), regional ileitis (a regional inflammatory condition of the terminal ileum), peptic ulceration (a condition of the stomach and duodenum) and irritable bowel syndrome; pyresis, pain;

and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor.

The compounds of the invention may be used on their own or in combination with other drugs, for example:

for the treatment, in particular, of colitis, Crohn's disease and psoriasis: steroids, particularly those steroids which are eliminated presystemically, salazopyrin, keratolytic agents such as salicylic acid or purified coal tar fractions, dithranol, vitamins, for example vitamins A, D or E, antifungal agents such as benzuldazic acid, hexetidine, enilconazole or other azole antifungals, natamycin, polynoxylin, providone-iodine, griseofulvin and 2,4,6-tribromotoluene;

for the treatment of eczema the compounds may be combined with steroids or with antipruritic agents such as crotamition;

for the treatment of acne the compounds may be combined with bezoyl peroxide or tretonin;

for the treatment of seborrheic dermatitis the compounds may be combined with selenium sulphide, coal tar fractions, zinc pyrithione, sulphur, salicylic acid or steroids;

for the treatment of rosacea the compounds may combined with sulphur, particularly in the form of an ointment.

For the above mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general satisfactory results are obtained when the compound is administered at a daily dosage of from about 0.1mg to about 60mg per kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man the total daily dose is in the range of from 7.0mg to 4.2g and unit dosage forms suitable for oral administration comprise from 2.0mg to 4.2g of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

Compounds of formula I, and pharmaceutically

acceptable derivatives thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral including topical, or parenteral administration. Thus the new compound may be compounded with inorganic or organic, pharmaceutically acceptable adjuvants, diluents or carriers. Examples of such adjuvants, diluents and carriers are:- for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose; for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural or hardened oils or waxes.

Compositions in a form suitable for oral, ie aqueous or non aqueous suspensions or semi-solid gels, oesophageal administration include pills, capsules and tablets; particular tablets that may be mentioned include enteric coated, dispensible, effervescent, chewable and formulations intended for sublingual and buccal absorbtion.

Compositions in a form suitable for administration to the lung include formulations in inhalers, atomizers, nebulizers or insufflators as aerosols, particularly pressurised aerosols;

Compositions for rectal administration include suppositories or enemas, composition for parenteral delivery by injection (intravenous, subcutaneous, intramuseable) include cosolvent solutions, suspensions,

emulsions, oils for parenteral delivery;

Compositions in a form suitable for topical administration to the skin include ointments, creams, oil-in-water emulsions or water-in-oil emulsion; aqueous or organic gels (for example celluloses or carboxyvinylpolymers).

compositions in a form suitable for topical administration to the eye or nose include solutions, suspensions, semi-solid gels, ointments and emulsions.

We prefer the composition to contain up to 50% and more preferably up to 25% by weight of the compound of formula I, or of the pharmaceutically acceptable derivative thereof.

The compound of formula I and pharmaceutically acceptable derivatives thereof have the advantage that they are less toxic, more efficacious, are longer acting, have a broader range of activity, are more potent, produce fewer side effects, more selective, are more easily absorbed, more stable or have other useful pharmacological properties, than compounds of similar structure.

The invention is illustrated by the following examples, in which temperatures are given in degrees celsius.

A. PREPARATION OF INTERMEDIATES

Example A

4-amino-2,6-dimethylphenyl acetate

To 2,6-dimethyl-4-nitrophenol (10g) and triethylamine (21ml) in dry dichloromethane (100ml) at 0° was added acetyl chloride (5.6ml) slowly. After 16 hours the mixture was washed with water, dried and evaporated to give the acetate (9.4g), mp 109-110°. The acetate (9.4g) was hydrogenated in ethanol at atmospheric pressure over platinum oxide for 4 hours. Filtration, evaporation, and crystallisation (ethyl acetate/hexane) of the residue gave the title acetate (5.6g), mp 82-83°.

Example B

4-amino-3,6-dimethoxy-2-methylphenol

Sulphanilic acid (10.8g) was diazotised as in "Organic Syntheses" Coll. Vol. 2, p 35. After 20 minutes the resulting suspension was added to an ice-cold solution of 3,6-dimethoxy-2-methylphenol (8.1g) and sodium hydroxide (10.8g) in water (100ml). After one hour the mixture was heated to 45-50° and sodium hydrosulphite (22.2g) was added in portions. When the red dye colour was discharged the mixture was cooled to give a yellow precipitate of the bisulphite salt (10g) of the title phenol.

Example C

Using the method of Example B above, the following phenols were prepared via their bisulphite salts:

a) 4-amino-2,6-dimethylphenol;

b) 4-amino-2,3,4,5-tetramethylphenol;

c) 4-amino-2,6-bis(1,1-dimethylethyl)phenol.

Example D

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenol

2,6-dimethyl-4-aminophenol (15g) and 4,5-dihydro-1-phenyl-1H-pyrazol-3-amine (17.6g) were heated with p-toluene sulphonic acid (0.2g) at 160° for 1 hour under nitrogen. The mix was cooled, taken up in dichloromethane and washed with dilute HCl, and water. Evaporation, and chromatography of the residue (silica, dichloromethane/ethyl acetate [9:1]) gave 4-(4,5-dihydro-1-phenyl-1H-pyrazol-3-yl)amino-2,6-dimethylphenol (14.2g), mp 154-158°. This was refluxed in toluene (40ml) with 10% palladium on charcoal (10g) for 3 hours. The mixture was filtered and evaporated to give, after crystallisation from cyclohexane/ethyl acetate, the title compound (8g), mp 154-155°.

Example E

The following intermediates were made by the method of Example D:

a) 2,3,5,6-tetramethyl-4-(1-phenyl-1H-pyrazol-3-yl)amino phenol, mp 160-162°;

b) 3,6-dimethoxy-2-methyl-4-(1-phenyl-1H-pyrazol-3-yl) aminophenol, mp 107-108°;

c) 2,6-bis(1,1-dimethylethyl)-3-(1-phenyl-1H-pyrazol-3-yl)

aminophenol, mp 114-115°;

d) 2,6-dichloro-4-(1-phenyl-1H-pyrazol-3-yl)aminophenol, mp 144-146°.

Example F

2,6-dimethyl-4-[N-methyl-N-(1-phenyl-1H-pyrazol-3-yl aminophenol

To 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)amino phenol (8g), acetic acid (2.8ml), and aqueous 40% formaldehyde (3.1ml) in acetonitrile (40ml) was added sodium cyanoborohydride (5.4g). After 2 hours the mixure was quenched with water and extracted with dichloromethane. The organic phase was washed with aqueous sodium bicarbonate solution, then water, dried, evaporated and chromatographed (silica, dichloromethane) to give the title product (3g), mp 139-140° (from ethanol).

Example G

The following intermediates was prepared by the method of Example F:

a) 2,6-bis(1,1-dimethylethyl)-4-[N-methyl-N-(1-phenyl-1H-pyrazol-3-yl)amino]phenol, mp 117-118°.

Example H

2-Ethylsulphinyl-6,7,8,9-tetrahydro-4H-1-naphtho [2,3-b]pyran-4-one

The title compound (mp 158-159°) was prepared from 1-(3-hydroxy-6,7,8,9-tetrahydronaphthalene-2-yl)ethanone by

condensation with carbon disulphide, alkylation with ethyl iodide, and oxidation according to the methods in J. Heterocyclic Chem., 1981, 18, 679.

Example I

5,6-Diethoxy-2-methylsulphonyl-1H-benzimidazole

The title compound (mp 182-184°) was prepared from 5,6-diethoxy-1,3-dihydro-2H-benzimidazole-2-thione by alkylation (methyl iodide) and oxidation.

Example J

The following were prepared from the appropriate amino heterocycle by the methods described in EP-A-254 259:

a) 2,6-dimethyl-4-(pyrazin-2-yl)aminophenol, mp 188-190°;

b) 4-(4-chloro-6-methylpyrimidin-2-yl)amino-2,6-dimethyl phenol, mp 160-163°.

B. PREPARATION OF COMPOUNDS OF FORMULA I

The following compounds of formula I were prepared from the intermediates described above or from compounds known in the art, including those described in EP-A-254 259 and EP-A-178 035.

Example 1

4-[4,5-Dihydro-1-phenyl-1H-pyrazol-3-yl]amino-2,6-dimethylphenyl acetate

4,5-Dihydro-1-phenyl-1H-pyrazol-3-amine (0.16g), 4-amino-2,6-dimethylphenyl acetate (0.2g), and toluene-4-sulphonic acid (0.02g) were refluxed in toluene

under nitrogen for 8 hours. Evaporation and chromatography (silica, dichloromethane/ethyl acetate [95:5]) of the residue gave the title product (0.15g), as a solid.

Example 2

Using the method of Example 1, the following compound was prepared:

a) 4-[4,5-Dihydro-1-(3-trifluoromethylphenyl)-1H-pyrazol-3-yl]amino-2,6-dimethylphenyl acetate, mp 190-191°.

b) 2,6-Dimethyl-4-[6,7,8,9-tetrahydro-4-oxo-4H-1-naphtho [2,3-b]pyran-2-yl]aminophenyl acetate, (from the intermediate sulphoxide of Example H)., mp 224 -226°

c) 4-(5,6-Diethoxy-1H-benzimidazol-2-yl)amino-2,6-dimethyl -phenyl acetate, (from the intermediate of Example I), mp 91-94°

d) 2,6-dimethyl-4-(quinolin-2-yl)aminophenyl acetate, (from 2-chloroquinoline), mp 154-155;

e) 4-(3-aminocarbonylpyridin-2-yl)amino-2,6-dimethylphenyl acetate, (from 2-chloronicotinamide), mp 209-211;

f) 2,6-dimethyl-4-(2-pyrimidinyl)aminophenyl acetate, (from 2-chloropyrimidine).

Example 3

4-(1-Phenyl-1H-pyrazol-3-yl)amino-2,6-di(prop-2-enyl) phenyl acetate

(a) 4-(1-Phenyl-1H-pyrazol-3-yl)amino-2-(prop-2-enyl) phenol

4-(1-Phenyl-1H-pyrazol-3-yl)aminophenyl (19g) was added to sodium hydride (4.0g of a 50% suspension, freed from oil) in dry dimethyl formamide (150ml). After 0.5 hr, allyl bromide (7.2ml) was added, and the mixture was stirred for 16 hours, poured into water, and extracted with ethyl acetate. Evaporation of solvent and chromatography (silica/dichloromethane) gave 1-phenyl-N-(4-[[prop-2-enyl]oxyphenyl)-1H-pyrazol-3-amine (21.9g), mp 80-81°. This solid (2.9g) was heated at 200° under nitrogen for 5 hours. Chromatography (silica/dichloromethane) gave the sub-title product as a viscous oil (1.4g). Salient ^{1}HNMR (DMSO) : δ 8.7 (1H, s, NH); 8.4 (1H, s, OH); 6.0 (1H, m, -CH=); 5.1 (2H, dd, $=CH_2$); 3.25 (2H, d, OCH_2).

(b) 4-(1-Phenyl-1H-pyrazol-3-yl)amino-2,6-di(prop-2-enyl)phenol

The sub-title product from (a) (10.5g) was converted by analogous processes to (a) to 1-phenyl-N-(3-[prop-2-enyl]-4-[prop-2-enyl]oxyphenyl)-1H- pyrazol-3-amine (7.6g, oil) and then to the sub-title phenol (5.5g), mp 87-88°.

(c) 4-(1-Phenyl-1H-pyrazol-3-yl)amino-2,6-di(prop-2-enyl)phenyl acetate

To the product from step (b) (5.0g) in dichloromethane (100ml) containing 4-dimethylaminopyridine (10mgs) and triethylamine (2.1ml) was added acetyl chloride (1.1ml) slowly with stirring. After 6 hours water was added, and

the residue after evaporation of the organic phase was chromatographed (silica/dichloromethane), and then crystallised from cyclohexane to afford the title product (4.5g), mp 110-111°.

Example 4

The following compounds were made by the method of Example 3c), from the corresponding phenol and appropriate carbonyl or sulphonyl chloride:

a) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl butanoate, mp 138-140°;

b) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 2,2-dimethylpropanoate, mp 139-140°;

c) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl phenyl carbonate, mp 138-139°;

d) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl methyl carbonate, mp 110-112°;

e) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl benzoate, mp 117-118°;

f) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl methanesulphonate, mp 144-145°;

g) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 2-methylpropanoate, mp 127-128°;

h) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl phenylmethyl carbonate, mp 105-106°;

i) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl

4-methoxybenzoate, mp 185-187°;

j) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl methoxyacetate, mp 149-150°;

k) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl chloroacetate, mp 141-142°;

l) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl (1,1-dimethylethyl)carbonate, mp 122-123°;

m) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 4-nitrobenzoate, mp 210-211°;

n) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl butyl carbonate, mp 72-73°;

o) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 3-pyridinecarboxylate, mp 158-160°;

p) 4-(4-Chloro-6-methylpyrimidin-2-yl)amino-2,6-dimethyl-phenyl acetate, mp 143-144°;

q) 4-(4-Chloro-6-methylpyrimidin-2-yl)amino-2,6-dimethyl-phenyl methoxyacetate, mp 126-127°;

r) 2,6-dimethyl-4-(pyrazin-2-yl)aminophenyl acetate, mp 176-177°;

s) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 4-chlorobenzoate, mp 166-167°;

t) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 3-methoxypropanoate, mp125-126°;

u) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl dimethylcarbamate, mp 171-173°;

v) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 4-dimethylamino-4-oxobutanoate, mp 210-211°;

w) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetoxyethanoate, mp 127-128°;

x) methyl 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl propanedioate, mp 112-113°;

y) methyl 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 1,5-pentanedioate, mp 108-109°;

z) methyl 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 1,4-butanedioate, mp 90-91°;

aa) 3,6-dimethoxy-2-methyl-4-(1-phenyl-1H-pyrazol-3yl)-aminophenyl acetate, mp 132-134°;

ab) 2,6-dimethyl-4-[N-methyl-N-(1-phenyl-1H-pyrazol-3-yl)]-aminophenyl ethanoate, mp 111-112°;

ac) 2,3,5,6-tetramethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetate, mp 179-180°;

ad) 2,6-dichloro-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetate, mp 169-170°;

ae) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl phenylmethoxyacetate, mp 101-101.5°;

af) 2,5-dimethoxy-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetate, mp 149-150°.

ag) Benzene-1,4-dicarboxylic acid, mono-[2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl] ester, mono-phenylmethyl ester, mp 169-171°.

Example 5

2,6-bis(1,1-dimethylethyl)-4-(N-methyl-N-[1-phenyl-1H-pyrazol-3-yl]amino)phenyl acetate

To 2,6-bis(1,1-dimethylethyl)-4-(N-methyl-N-[1-phenyl-1H-pyrazol-3-yl]amino)phenol (0.6g) in dry tetrahydrofuran (15ml) at -78° under nitrogen was added butyl lithium (1.29 ml of 1.4M hexane solution). After 10 minutes acetyl chloride (0.2ml) was added. The reaction was left for 16 hours, poured into water and extracted with ethyl acetate. Evaporation, and chromatography (silica, dichloromethane/hexane [1:1]) of the residue, followed by recrystallisation from hexane at -20° gave the title compound (0.35g), mp 102-103°.

Example 6

Using the appropriate acyl chlorides and phenols, the following compounds were prepared by the method of Example 5:

a) 2,6-bis(1,1-dimethylethyl)-4-(N-methyl-N-[1-phenyl-1H-pyrazol-3-yl]amino)phenyl methoxyacetate, mp 102-103°;

b) 2,6-bis-(1,1-dimethylethyl)-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetate, mp 186-187°; position of acetyl confirmed by NOE difference spectrum.

2,6-bis(1,1-dimethylethyl)-4-[(1-methyl-1H-pyrazol-3-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(2-oxazolylamino)-phenyl

acetate

4-[(6-chloropyrazinyl)amino]-2,6-bis(1,1-dimethylethyl)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-1,2,3-triazol-4-yl amino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(4-pyrimidinylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(4-methyl-2-pyrimidinyl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(2-pyrimidinylamino)-phenyl acetate

4-[(3,6-dichloro-4-pyridazinyl)amino]-2,6-bis(1,1-dimethylethyl)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(4-pyridazinylamino)-phenyl acetate

6-[[3,5-bis(1,1-dimethylethyl)-4-acetoxyphenyl]amino]-3-pyridazinemethanol phenyl acetate

4-[(6-chloro-3-pyridazinyl)amino]-2,6-bis(1,1-dimethyl)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(6-ethoxy-3-pyridazinyl amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(6-methyl-3-pyridazinyl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(3-pyridazinylamino)-phenyl acetate

2,6-(1,1-dimethylethyl)-6-(1-methylethyl)-4-(pyrazinyl amino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(4H-1,2,4-triazol-4-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(pyrazinylamino)-phenyl acetate

2,6-dimethyl-4-(pyrazinylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-imidazol-2-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(3-phenyl-1,2,4-thia diazol-5-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1,2,4-triazin-3-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(2-methyl-3-thienyl) amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(5-methyl-1,3,4-thia diazol-2-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(1-methyl-1H-pyrazol-5-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-pyrazol-3-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(pyrazinylamino)-phenyl acetate

4-[(4-amino-5-pyrimidinyl)amino]-2,6-bis(1,1-dimethyl ethyl)-phenyl acetate

2,6-bis(1-methylethyl)-4-(pyrazinylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(6-methoxypyrazinyl) amino]-phenyl acetate

Methyl 6-[[3,5-bis(1,1-dimethylethyl)-4-acetoxy phenyl]amino]-3-pyridazinecarboxylate

2,6-bis(1,1-dimethyl)-4-[(6-methoxy-3-pyridazinyl) amino]-phenyl acetate

Methyl 5-[[3,5-bis,(1,1-dimethylethyl)-4-hydroxy phenyl]amino]-pyrazinecarboxylate

2,6-bis(1,1-dimethylethyl)-4-[(5-phenylpyrazinyl)amino] -phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(5-methylpyrazinyl)amino] -phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(5-pyrimidinylamino)- phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(4-pyridazinylamino)- phenyl acetate

2-(1,1-dimethylethyl)-6-(1-methylethyl)-4-(3- pyridazinylamino)-phenyl acetate

2,3,6-trimethyl-4-(pyrazinylamino)-phenyl acetate

4-[(6-chloro-4-pyrimidinyl)amino]-2,6-bis(1,1-dimethyl ethyl)-phenyl acetate

5-[[3,5-bis(1,1-dimethylethyl)-4-acetoxyphenyl]amino]- pyrazinemethanol

2,3,6-trimethyl-4-(2-pyrimidinylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(4,6-dimethyl-2-pyrimidinyl)amino]-phenyl acetate

2-(1,1-dimethylethyl)-6-(1-methylethyl)-4-(1H-pyrazol-3-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-1,2,4-triazol-3-ylamino)-phenyl acetate

2,6-bis(1,1-dimethyl)-4-[(2-methyl-2H-1,2,3-triazol-4-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(1-methyl-1H-1,2,3-triazol-4-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(5-methyl-3-isoxazoly)amino]-phenyl acetate

Methyl 2-thiophenecarboxylate 3-[[3,5-bis(1,1-dimethylethyl)-4-acetoxyphenyl]amino]-phenyl acetate

2-6-bis(1,1-dimethylethyl)-4-[(1-methyl-1H-pyrazol-4-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-[pyrazol-4-ylamino)-phenyl acetate

Ethyl 1H-pyrazol-4-carboxylate 5-[[3,5-bis(1,1-dimethylethyl)-4-acetoxyphenyl]amino]-1-methyl

2,6-bis(1,1-dimethylethyl)-4-[(1,3-diphenyl-1H-pyrazol-5-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[((1-methyl-3-phenyl-1H-pyrazol-5-yl]amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(1-propyl-1H-pyrazol-5-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(1-propyl-1H-pyrazol-3-yl)amino]-phenyl acetate

2,3,6-trimethyl-4-(1H-pyrazol-3-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(6-methyl-3-pyridazinyl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(pyrazinylamino)-phenyl acetate N-oxide

2,6-bis(1,1-dimethylethyl)-4-[(2-methyl-3-thienylamino]-phenyl acetate

2,6-bis(1,1-dimethylethyl-4-[(5,6-dimethyl-1,2,4-triazin-3-ylamino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1,3,4-thiadiazol-2-yl amino]-phenyl acetate

2,6-bis(methylethyl)-4-(1H-pyrazol-3-ylamino)-phenyl acetate

Example 7

1,4-Butanedioic acid, mono(2,6-dimethyl-4-[1-phenyl-1H-pyrazol-3-yl]aminophenyl) ester

To 4-(1-phenyl-1H-pyrazol-3-yl)amino-2,6-dimethyl phenol (1.8g) in dry dichloromethane (30ml) and triethylamine (2.25ml) at 0° under nitrogen was added succinic anhydride (0.84g). The mixture was stirred at

room temperature for 16 hours then poured into water. The organic phase was dried and evaporated. The resultant oil was chromatographed (silica, 2% methanol/dichloromethane) to give the title product (1.5g), mp 160-161° after crystallisation from hexane/ethyl acetate.

Example 8

The following compound was prepared by the method of Example 7:

a) 1,5-pentanedioic acid, mono(2,6-dimethyl-4-[1-phenyl-1H-pyrazol-3-yl]aminophenyl ester, mp 138-140°;

Example 9

2,6-Dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 2-oxopropanoate

1,1'-carbonyldiimidazole (4.9g) was added batchwise to pyruvic acid (2.6g) in dichloromethane (100ml), and after 0.5 hours 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl) aminophenol (2.8g) was added. The mixture was left for 16 hours, then evaporated, and the residue was chromatographed (silica, dichloromethane) to give, after crystallisation (hexane/ethyl acetate), the title product (1.0g) mp 123-125°.

Example 10

The following compounds were prepared by the method of Example 9:

a) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl

N-[(phenylmethoxy)carbonyl]glycinate, mp142-143°;

b) 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 4-dimethylaminobutanoate, mp 83-85°.

Example 11

2,6-Dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetate

The product from Example 1 was refluxed in toluene with 5% palladium on charcoal (0.15g) for 4 hours. Filtration, evaporation and chromatography (silica, dichloromethane/ethyl acetate [95:5]) of the residue gave the title compound (0.07g), mp 114-116° (from cyclohexane); further polymorph, mp 134°.

Analysis found: C, 71.2%; H, 6.1; N, 12.85%

Calculated for $C_{19}H_{19}N_3O_2$: C, 70.9; H, 5.9; N, 12.5%.

Example 12

The following compound was prepared from the compound of Example 2a by the method of Example 11:

2,6-Dimethyl-4-(1-[3-trifluromethylphenyl]-1H-pyrazol-3-yl)aminophenyl acetate, mp 142-143°.

Example 13

4-(1-Phenyl-1H-pyrazol-3-yl)amino-2,6-dipropylphenyl acetate

4-(1-Phenyl-1H-pyrazol-3-yl)amino-2,6-di(prop-2-enyl) phenyl acetate, from Example 3b), (3.5g) in ethanol (150ml)

was hydrogenated at atmospheric pressure over 10% palladium on charcoal to afford, after crystallisation from cyclohexane, the title product (1.8g), mp 71-74°.

Example 14

Using the method of Example 13, the following compounds were obtained from the indicated precursors:

a) 2,6-Dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl hydroxyacetate, mp 155-157°

b) 4-(1-Cyclohexyl-1H-pyrazol-3-yl)amino-2,6-dimethylphenyl hydroxyacetate, mp 160-164°

a) and b) were prepared from 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl phenylmethoxyacetate by hydrogenation at 5 atmospheres for 6 days and separation of the resulting mixture of compounds by chromatography (silica, dichloromethane/ethyl acetate (9:1)).

c) 2,6-Dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl glycinate hydrochloride, prepared from Example 10a and followed by treatment with ethereal hydrogen chloride, mp 230-231°

d) Benzene-1,4-dicarboxylic acid, mono-[2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl] ester, prepared from the monobenzyl ester, from the example 4ag) mp 221-222°.

Example 15

2,6-Dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl cyanoacetate

2,6-Dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl chloroacetate, Example 4k, (1g) and sodium cyanide (0.5g) stirred in dimethyl sulphoxide for 16 hours gave, after dilution with brine, extraction with ethyl acetate and subsequent evaporation, the title compound (0.3g), mp 116-117° (from ethyl acetate/hexane).

Example 16

3-[2,6-Dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)amino-phenoxycarbonyl]-1-methylpyridinium iodide

2,6-Dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 3-pyridinecarboxylate, Example 4o), (0.5g) was refluxed in methyl iodide (100ml) for 4 days, the unreacted methyl iodide removed by evaporation and the title product (0.15g) obtained by trituration of the resulting oil with ether, mp 150°(dec).

Example 17 - Compositions

a) For topical delivery to the skin

Cosolvent type gel for topical application:

Active ingredient	0.5%
Hydroxypropyl cellulose	1.0%
Ethanol	90.0%
Water	to 100.0%

b) Ophthalmic delivery

Active ingredient (micronized)	2.0%
Carbopol 934P	1.0%

Sodium hydroxide	to pH7
Benzalkonium chloride	0.01%
NaCl	0.9%
Water	to 100.0%

c) Enema for rectal delivery

Active ingredient (micronized	3.0%
Glycerol	2.5%
Methyl parabens	0.15%
Propyl parabens	0.15%
Water	to 100.0%

d) Subcutaneous oily injection

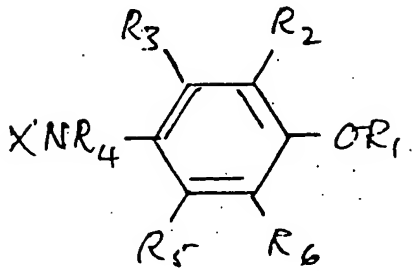
Active ingredient	3.0%
Miglyol 812 N	to 100.0%

e) Nasal suspension

Active ingredient (micronized)	1.0%
Polysorbate 80	0.5%
Benzalkonium chloride	0.01%
Glycerol	2.4%
Avicel	2.0%
Water	to 100.0%

We claim:

1. Compounds of formula I,



I

in which

R_1 represents C(O)YZ or SO_2R_{10},

Y represents a single bond, O, NR_{11} or CO,

Z represents hydrogen, alkyl or alkyl substituted by one or more substituents selected from hydroxy, alkoxy, acyloxy, carboxy, alkoxycarbonyl, $CONR_{12}R_{13}$, arylalkoxy, Ar_1, heterocycle, halo, cyano or $NR_{14}R_{15}$,

R_2, R_3, R_5 and R_6, which may be the same or different, represent hydrogen, alkyl, alkoxy or halogen,

R_4 and R_{11}, which may be the same or different, represent hydrogen or alkyl,

R_{10} represents alkyl,

X represents a heterocycle optionally substituted by one or more substituents selected from alkyl, cycloalkyl, alkoxy, alkoxycarbonyl, carboxy, hydroxyalkyl, halo, $CONR_{16}R_{17}$, $NR_{18}R_{19}$, or Ar_2,

Ar_1 and Ar_2, which may be the same or different, represent aryl or aryl substituted by one or more

substituents selected from halogen, nitro, alkoxy, carboxy, alkyl or trihaloalkyl, R_{12}, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{18} and R_{19}, which may be the same or different, represent hydrogen, alkyl or benzyloxycarbonyl,

or a pharmaceutically acceptable N-oxide, N-alkyl, salt, ester or amide derivative thereof,

for use as a pharmaceutical.

2. A compound of formula I or a derivative thereof, as defined in Claim 1, provided that at least one of R_2 and R_6 is other than hydrogen.

3. A compound according to Claim 2, wherein R_1 represents C(O)Z.

4. A compound according to Claim 2 or Claim 3, wherein R_2 and R_6 both represent alkyl.

5. A compound according to any one of Claims 2 to 4, wherein R_3 and R_5 both represent hydrogen.

6. A compound according to any of Claims 2 to 5, wherein X represents a 5- or 6- membered heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur, optionally substituted by one or more substituents selected from alkyl, alkoxy, alkoxycarbonyl, carboxy, hydroxyalkyl, halo, $CONH_2$, NH_2 or Ar_2.

7. A compound according to any of Claims 2 to 6, wherein X represents pyrazole optionally substituted by Ar_2.

8. A compound of formula I, which is 2,6-dimethyl-4-

(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetate, or a pharmaceutically acceptable salt thereof.

9. A compound of formula I, which is

4-[4,5-dihydro-1-phenyl-1H-pyrazol-3-yl]amino-2,6-dimethylphenyl acetate,

4-[4,5-dihydro-1-(3-trifluoromethylphenyl)-1H-pyrazol-3-yl]amino-2,6-dimethylphenyl acetate,

2,6-dimethyl-4-[6,7,8,9-tetrahydro-4-oxo-4H-1-naphtho[2,3-b]pyran-2-yl]aminophenyl acetate,

4-(5,6-diethoxy-1H-benzimidazol-2-yl)amino-2,6-dimethyl-phenyl acetate,

2,6-dimethyl-4-(quinolin-2-yl)aminophenyl acetate,

4-(3-aminocarbonylpyridin-2-yl)amino-2,6-dimethylphenyl acetate,

2,6-dimethyl-4-(2-pyrimidinyl)aminophenyl acetate,

4-(1-phenyl-1H-pyrazol-3-yl)amino-2,6-di(prop-2-enyl)phenyl acetate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl butanoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 2,2-dimethylpropanoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl phenyl carbonate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl methyl carbonate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl benzoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl methanesulphonate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 2-methylpropanoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl phenylmethyl carbonate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 4-methoxybenzoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl methoxyacetate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl chloroacetate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl (1,1-dimethylethyl)carbonate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 4-nitrobenzoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl butyl carbonate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 3-pyridinecarboxylate,

4-(4-Chloro-6-methylpyrimidin-2-yl)amino-2,6-dimethyl-phenyl acetate,

4-(4-Chloro-6-methylpyrimidin-2-yl)amino-2,6-dimethyl-

phenyl methoxyacetate,

2,6-dimethyl-4-(pyrazin-2-yl)aminophenyl acetate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 4-chlorobenzoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 3-methoxypropanoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl dimethylcarbamate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 4-dimethylamino-4-oxobutanoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetoxyethanoate,

methyl 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl propanedioate,

methyl 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 1,5-pentanedioate,

methyl 2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 1,4-butanedioate,

3,6-dimethoxy-2-methyl-4-(1-phenyl-1H-pyrazol-3yl)-aminophenyl acetate,

2,6-dimethyl-4-[N-methyl-N-(1-phenyl-1H-pyrazol-3-yl)]-aminophenyl ethanoate,

2,3,5,6-tetramethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetate,

2,6-dichloro-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl

acetate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl phenylmethoxyacetate,

2,5-dimethoxy-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetate,

benzene-1,4-dicarboxylic acid, mono-[2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl] ester, mono-phenylmethyl ester,

2,6-bis(1,1-dimethylethyl)-4-(N-methyl-N-[1-phenyl-1H-pyrazol-3-yl]amino)phenyl acetate,

2,6-bis(1,1-dimethylethyl)-4-(N-methyl-N-[1-phenyl-1H-pyrazol-3-yl]amino)phenyl methoxyacetate,

2,6-bis-(1,1-dimethylethyl)-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl acetate,

2,6-bis(1,1-dimethylethyl)-4-[(1-methyl-1H-pyrazol-3-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(2-oxazolylamino)-phenyl acetate

4-[(6-chloropyrazinyl)amino]-2,6-bis(1,1-dimethylethyl)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-1,2,3-triazol-4-yl amino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(4-pyrimidinylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(4-methyl-2-pyrimidinyl)

amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(2-pyrimidinylamino)-phenyl acetate

4-[(3,6-dichloro-4-pyridazinyl)amino]-2,6-bis(1,1-dimethylethyl)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(4-pyridazinylamino)-phenyl acetate

6-[[3,5-bis(1,1-dimethylethyl)-4-acetoxyphenyl]amino]-3-pyridazinemethanol phenyl acetate

4-[(6-chloro-3-pyridazinyl)amino]-2,6-bis(1,1-dimethyl)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(6-ethoxy-3-pyridazinyl amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(6-methyl-3-pyridazinyl) amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(3-pyridazinylamino)-phenyl acetate

2,6-(1,1-dimethylethyl)-6-(1-methylethyl)-4-(pyrazinyl amino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(4H-1,2,4-triazol-4-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(pyrazinylamino)-phenyl acetate

2,6-dimethyl-4-(pyrazinylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-imidazol-2-ylamino)-

phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(3-phenyl-1,2,4-thiadiazol-5-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1,2,4-triazin-3-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(2-methyl-3-thienyl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(5-methyl-1,3,4-thiadiazol-2-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(1-methyl-1H-pyrazol-5-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-pyrazol-3-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(pyrazinylamino)-phenyl acetate

4-[(4-amino-5-pyrimidinyl)amino]-2,6-bis(1,1-dimethylethyl)-phenyl acetate

2,6-bis(1-methylethyl)-4-(pyrazinylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(6-methoxypyrazinyl)amino]-phenyl acetate

Methyl 6-[[3,5-bis(1,1-dimethylethyl)-4-acetoxyphenyl]amino]-3-pyridazinecarboxylate

2,6-bis(1,1-dimethyl)-4-[(6-methoxy-3-pyridazinyl)amino]-phenyl acetate

Methyl 5-[[3,5-bis,(1,1-dimethylethyl)-4-hydroxy phenyl]amino]-pyrazinecarboxylate

2,6-bis(1,1-dimethylethyl)-4-[(5-phenylpyrazinyl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(5-methylpyrazinyl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(5-pyrimidinylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(4-pyridazinylamino)-phenyl acetate

2-(1,1-dimethylethyl)-6-(1-methylethyl)-4-(3-pyridazinylamino)-phenyl acetate

2,3,6-trimethyl-4-(pyrazinylamino)-phenyl acetate

4-[(6-chloro-4-pyrimidinyl)amino]-2,6-bis(1,1-dimethyl ethyl)-phenyl acetate

5-[[3,5-bis(1,1-dimethylethyl)-4-acetoxyphenyl]amino]-pyrazinemethanol

2,3,6-trimethyl-4-(2-pyrimidinylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(4,6-dimethyl-2-pyrimidin yl)amino]-phenyl acetate

2-(1,1-dimethylethyl)-6-(1-methylethyl)-4-(1H-pyrazol-3-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-1,2,4-triazol-3-yl amino)-phenyl acetate

2,6-bis(1,1-dimethyl)-4-[(2-methyl-2H-1,2,3-triazol-4-

yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(1-methyl-1H-1,2,3-triazol-4-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(5-methyl-3-isoxazolyl)amino]-phenyl acetate

Methyl 2-thiophenecarboxylate 3-[[3,5-bis(1,1-dimethylethyl)-4-acetoxyphenyl]amino]-phenyl acetate

2-6-bis(1,1-dimethylethyl)-4-[(1-methyl-1H-pyrazol-4-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1H-[pyrazol-4-ylamino)-phenyl acetate

Ethyl 1H-pyrazol-4-carboxylate 5-[[3,5-bis(1,1-dimethylethyl)-4-acetoxyphenyl]amino]-1-methyl

2,6-bis(1,1-dimethylethyl)-4-[(1,3-diphenyl-1H-pyrazol-5-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[((1-methyl-3-phenyl-1H-pyrazol-5-yl]amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(1-propyl-1H-pyrazol-5-yl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(1-propyl-1H-pyrazol-3-yl)amino]-phenyl acetate

2,3,6-trimethyl-4-(1H-pyrazol-3-ylamino)-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-[(6-methyl-3-pyridazinyl)amino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(pyrazinylamino)-phenyl acetate N-oxide

2,6-bis(1,1-dimethylethyl)-4-[(2-methyl-3-thienylamino]-phenyl acetate

2,6-bis(1,1-dimethylethyl-4-[(5,6-dimethyl-1,2,4-triazin-3-ylamino]-phenyl acetate

2,6-bis(1,1-dimethylethyl)-4-(1,3,4-thiadiazol-2-yl amino]-phenyl acetate,

2,6-bis(methylethyl)-4-(1H-pyrazol-3-ylamino)-phenyl acetate,

1,4-butanedioic acid, mono(2,6-dimethyl-4-[1-phenyl-1H-pyrazol-3-yl]aminophenyl) ester,

1,5-pentanedioic acid, mono(2,6-dimethyl-4-[1-phenyl-1H-pyrazol-3-yl]aminophenyl ester,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 2-oxopropanoate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl N-[(phenylmethoxy)carbonyl]glycinate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl 4-dimethylaminobutanoate,

2,6-dimethyl-4-(1-[3-trifluromethylphenyl]-1H-pyrazol-3-yl)aminophenyl acetate,

4-(1-phenyl-1H-pyrazol-3-yl)amino-2,6-dipropylphenyl acetate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl

hydroxyacetate,

4-(1-cyclohexyl-1H-pyrazol-3-yl)amino-2,6-dimethylphenyl hydroxyacetate,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl glycinate,

benzene-1,4-dicarboxylic acid, mono-[2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl] ester,

2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)aminophenyl cyanoacetate,

3-[2,6-dimethyl-4-(1-phenyl-1H-pyrazol-3-yl)amino-phenoxycarbonyl]-1-methylpyridinium iodide,

or a pharmaceutically acceptable salt of any one thereof.

10. A pharmaceutical composition comprising a compound of Formula I, as defined in Claim 1, or a pharmaceutically acceptable N-oxide, N-alkyl, salt, ester or amide therof, in association with a pharmaceutically acceptable carrier, diluent or adjuvant.

11. A method for the preparation of a compound of according to any one of Claims 2 to 9, or a pharmaceutically acceptable N-oxide, N-alkyl, salt, ester or amide derivative thereof,

which comprises

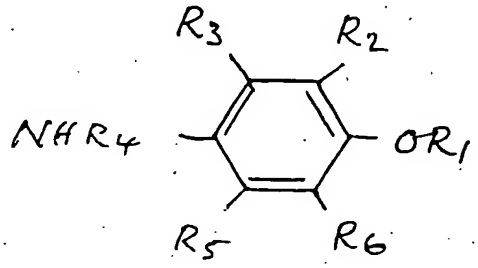
a) reacting a compound of formula II,

$$X\text{-}L_1 \qquad \text{II}$$

in which L_1 is a leaving group and

X is as defined in Claim 1,

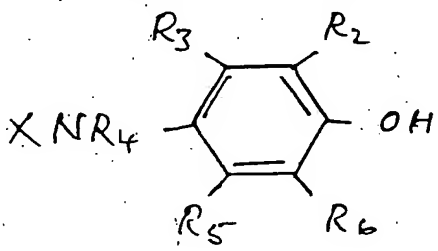
with a compound of formula III,



III

in which R_1, R_2, R_3, R_4, R_5 and R_6 are as defined in Claim 1,

b) reacting a compound of formula IV,



IV

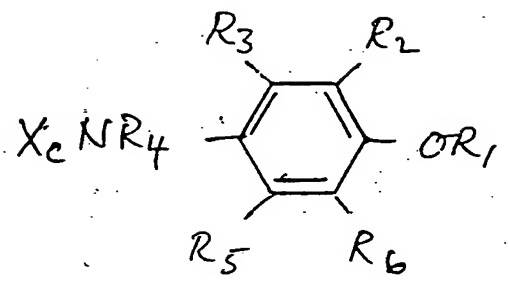
in which X, R_2, R_3, R_4, R_5 and R_6 are as defined in Claim 1,

with a compound of formula V,

$$R_1L_2 \qquad V$$

in which L_2 is a leaving group and R_1 is as defined Claim 1,

c) producing a compound of formula I in which X represents an unsaturated heterocycle, by oxidising a corresponding compound of formula VI,



in which Xc represents a corresponding heterocycle more saturated than X,

and R_1, R_2, R_3, R_4, R_5 and R_6 are as defined in Claim 1,

d) producing a compound of formula I which bears one or more alkyl substituents containing at least two carbon atoms, by reducing a corresponding compound of formula I, in which the appropriate substituent(s) contains one or more double or treble carbon-carbon bonds,

e) producing a compound of formula I, in which X is substituted by cyclohexyl, by reducing a corresponding compound of formula I in which X is substituted by phenyl.

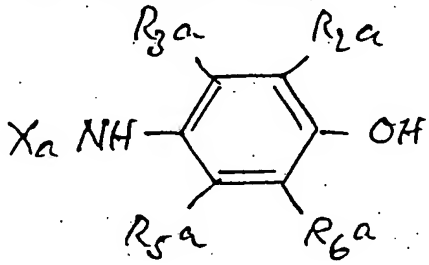
f) producing a compound of formula I substituted by one or more of OH, NHR_{14} or COOH, which comprises removing a protecting group from a corresponding compound of formula I bearing a protected OH, NHR_{14} or COOH group.

g) producing a compound of formula I, in which Z represents alkyl substituted by cyano, by reacting a corresponding compound of formula I in which Z represents alkyl substituted by halogen, with a cyanide salt,

h) producing a compound of formula I, which is a N-alkyl salt, by reacting a corresponding compound of formula I in which X represents a nitrogen containing heterocycle, with an alkylating agent,

and where necessary or desired converting the resulting compound of formula I to a pharmaceutical derivative thereof, or vice versa.

12. Compounds of formula IVa,



IVa

in which X_a represents 1H-pyrazol-3-yl substituted by 1-phenyl or 1-trifluromethylphenyl, R_2a and R_6a, which may be the same or different, are selected from lower alkyl, halogen and lower alkoxy, and both R_3a and R_5a represent hydrogen.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 90/00762

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC^5: C 07 D 231/06, A 61 K 31/415, C 07 D 231/38, C 07 D 213/82

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC^5	C 07 D 231/00, A 61 K 31/00, C 07 D 213/00, C 07 D 215/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, 11 with Indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
A	EP, A, 0127371 (FISONS PLC) 5 December 1984 --	
A	EP, A, 0248523 (FISONS PLC) 9 December 1987 --	
A	US, A, 4614742 (NOBUO ISHIKAWA et al.) 30 September 1986 --	
A	GB, A, 321738 (I.G. FARBENINDUSTRIE AG) 12 December 1929 --	
A	US, A, 3435041 (A.E. DRUKKER et al.) 25 March 1969 --	
A	US, A, 1810267 (K. DESAMARI) 16 June 1931 --	
A	US, A, 3853895 (G. LAMM et al.) 10 December 1974 --	

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* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20th August 1990	03. 10. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme N. KUIPER

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US, A, 4383851 (R.B. ROGERS et al.) 17 May 1983 --	
A	EP, A, 0067630 (SANKYO CO. LTD) 22 December 1982 --	
A	EP, A, 0013143 (ICI AUSTRALIA LTD) 9 July 1980 --	
A	US, A, 2748122 (R.R. BURTNER) 29 May 1956 --	
A	EP, A, 0126254 (CIBA-GEIGY AG) 28 November 1984 --	
A	EP, A, 0224339 (KUMIAI CHEMICAL INDUSTRY CO. LTD) 3 June 1987 --	
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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V[XX] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND : partially unsearchable.

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ..... because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers *) ..., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

*) Claims: 1-7,10,11. As the drafting of the claims is not clear and concise (Art.6,PCT) and encompasses such an enormous amount of products, a complete search is not possible on economic grounds (Art.17(2)(a)(ii),PCT). So the search has been limited to the examples.

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING :

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9000762 SA 36997

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 21/09/90
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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